Response to the Comment on ''Injury or Function—What Is Best to Assess Organ Viability Before Liver Graft Implantation?''

Reply:

We read with interest the letter by Patrono et al regarding our recent article in *Annals of Surgery* on viability testing during hypothermic oxygenated perfusion (HOPE) of liver grafts.[1] The authors of the letter present their results in 35 machine perfused livers (3 donation after circulatory death (DCD), 32 donation after brain death (DBD)), where they analyzed perfusate pH, glucose, lactate, and cytosolic enzymes during dual HOPE before liver transplantation. They raised some questions regarding the predictive value of flavin mononucleotide (FMN) compared with other classical markers.

Although we agree that the liver enzyme concentrations obtained from machine perfusates during HOPE or dual HOPE, as well as during normothermic machine liver perfusion, often do correlate with serum peak transaminases after graft implantation,[1,2] we contend that the prediction of liver function—instead of injury—is superior for the decision to use or not high-risk liver grafts.[1,2] We have therefore focused our perfusate analysis on surrogate markers of liver metabolism during HOPE treatment, performed on extended human DCD livers (n = 35/54).[1]

Within the first 60 minutes of HOPE, FMN is released from mitochondria, due to an electron overflow at complex I[3], depending on the metabolic liver status at start of perfusion. The detection of flavin in perfusates can therefore be considered as a functional marker of the mitochondrial electron chain, which is in direct contrast to simple release of cytosolic enzymes as a consequence of membrane rupture of cells. In addition, we have observed, that flavin release correlated with decreased synthesis of adenosine triphosphate, based on an impaired mitochondrial complex I–V function.[3] Of note, mitochondrial recovery has been recently identified as decisive for organ viability.[4] Consistently, perfusate FMN is highly predictive for liver graft function, as shown by correlation of FMN with International normalized ratio (INR) and factor V recovery after liver implantation. This finding appears novel and is in contrast to the rather weak correlation of conventional perfusate markers, including liver transaminases (Aspartate transaminase (AST), Alanine transaminase (ALT)), lactate (Supplementary Table 2),[1] and other glycolytic parameters.[5,6]

We agree, however, that the correlation of FMN with liver function and graft survival after implantation requires further validation in other transplant cohorts, which is currently performed by several European and American transplant centers. Of note, perfusate FMN measurement is a simple and quick technique, representing a cumulative measurement of the metabolic status of the whole liver graft, and can also be determined from stored samples by fluorimetric assays.

Muller Xavier, MD
Department of Surgery and Transplantation, Swiss HPB Centre, University Hospital Zurich, Zurich, Switzerland

Schlegel Andrea, MD
The Liver Unit, Queen Elizabeth Hospital Birmingham, Edgbaston, Birmingham, United Kingdom

Clavien Pierre-Alain, MD, PhD
Department of Surgery and Transplantation, Swiss HPB Centre, University Hospital Zurich, Zurich, Switzerland

Philipp Dutkowski, MD✉
Department of Surgery and Transplantation, Swiss HPB Centre, University Hospital Zurich, Zurich, Switzerland.
✉philipp.dutkowski@usz.ch

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The authors declare no conflicts of interest.

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